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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,259	02/20/2004	Kenichiro Hasumi	358690-00005-1	7322

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
03/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/783,259	HASUMI ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-15* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,8 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed on 10 September 2007 and supplemental to the Office Action mailed on 16 November 2007. Claim 2 is cancelled. Claims 1 and 3-15 are pending. Claims 3-5, 7, 8 and 12-15 are withdrawn. Claims 1, 6 and 9-11 are currently examined.

Where an Office action contains some other error that affects applicant's ability to reply to the Office action and this error is called to the attention of the Office within 1 month of the mail date of the action, the Office will restart the previously set period for reply to run from the date the error is corrected, if requested to do so by applicant. MPEP §710.06 [R-6].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Upon further review of the prior art, the rejection of claims 1, 6 and 9-11 under 35 U.S.C. §103(a) as being obvious over Baxevanis *et al.* (1997) in view of Meidenbauer *et al.* (2000), Setaluri *et al.* (US 2002/0192727) and Mengozzi *et al.* (2001) is **replaced by** the following **new ground of rejection**:

Claims 1, 6 and 9-11 are rejected under 35 U.S.C. §103(a) as being unpatentable over Baxevanis *et al*. (1997) in view of Meidenbauer *et al*. (2000), June *et al*. (1989) and Setaluri *et al*. (US 2002/0192727).

The instant claims are directed to a method of enhancing an immune response to an antigen in a mammal comprising administering lymphocyte conditioned media (LCM) derived from naïve T cells cultured with anti-CD3- and anti-CD28-coated beads in combination with a vaccine of said antigen to said mammal. Claim 6 limits the antigen to a prostate-specific antigen (PSA).

Meidenbauer *et al*. disclose a method of enhancing an immune response to an antigen, PSA, by administering a PSA-based vaccine in combination with an adjuvant, which is granulocyte-macrophage colony-stimulating factor (GM-CSF) or light mineral oil (page 89, 2nd column, to page 90). Meidenbauer *et al*. do not disclose administering LCM derived from naïve T cells cultured with antiCD3- and antiCD28-coated beads. Meidenbauer *et al*. do not disclose the dose and schedule of administration of the PSA with an adjuvant, either.

Baxevanis *et al*. describe a method of enhancing an immune response of tumor-antigen-specific lymphocytes by infusing back to the patients the supernatants collected from cultures of anti-CD3 monoclonal antibody-stimulated peripheral blood mononuclear cells (PBMC) (which contain naïve T cells) (page 1072, 2nd column, to page 1073 and page 1075, left column, Preparation of ACD3S). This method induced anti-tumor cytotoxic responses in clinical trials (page 1072, last sentence). Baxevanis *et al*. do not describe beads coated with both anti-CD3 and anti-CD28 monoclonal antibodies (mAb)

for T cell activation and are silent on the combination of prostate-specific antigen (PSA) with the activated PBMC supernatant.

June *et al*. disclose stimulation of IL-2 expression in T cells with anti-CD3 mAb or anti-CD28 mAb and describe that anti-CD28 mAb stimulation results in IL-2 concentrations that exceed 1000 U/ml in tissue culture supernatants and suggest that a role *in vivo* for anti-CD28 might be to amplify immune response initiated by the CD3/T cell receptor complex. See Abstract, page 156, Figure 2, and page 159, Figure 7. June *et al*. conclude that the signal delivered by anti-CD28 is able to synergize with "membrane bypass" signals that are generated by anti-CD3 stimulation and that occupancy of the anti-CD3/T cell receptor complex is not required to deliver the anti-CD28 signal, and furthermore, that anti-CD28 does not merely enhance signal transduction through anti-CD3 by acting as a Scaffold to enhance or prolong signaling through the antigen receptor. See page 159, 2nd column.

Setaluri *et al*. describe the dosage calculation and the administration of a tumor antigen hourly, daily, weekly, monthly, or yearly, by intramuscular or intravenous injection. See column 10, ¶90 and 92.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Meidenbauer *et al*. by substituting the adjuvant with the supernatants collected from *ex vivo* anti-CD3 activated PBMC, as taught by Baxevanis *et al*., and anti-CD28 costimulation, as taught by June *et al*. and adapting the dosage calculation, administration route and schedule taught by Setaluri *et al*. The skilled artisan would have been motivated to do so to increase the efficiency of

activation of T cell immune response and the immunogenicity of the tumor antigen, by enhancing NK cell-mediated cytotoxicity, and activating the up-regulation of IL-2-specific receptor, cytokine synthesis and secretion, cell proliferation and acquisition of both antigen-specific and antigen-non-specific T- lymphocyte cytotoxicity, as taught by Baxevanis *et al*. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the activation procedure of Baxevanis *et al*. by replacing the immobilized anti-CD3 antibodies with anti-CD3 and anti-CD28-coated beads for co-stimulation of naïve T cells, as suggested by June *et al*. The skilled artisan would have been motivated to do so to increase the amount of IL-2 concentration in tissue culture supernatants, which would make the supernatants a more potent adjuvant. There would have been a reasonable expectation of success, given that supernatants harvested from PBMC cultures stimulated with soluble anti-CD3 have been demonstrated to induce autologous lymphocytes *ex vivo* to display durable anti-tumor cytotoxic responses in clinical trials, as taught by Baxevanis *et al*., given the significant production of IL-2 in human T lymphocytes supernatants after anti-CD3/CD28 stimulation, as taught by June *et al*., and given the standard art-recognized dose and schedule for administration of an anti-tumor antigen, as taught by Setaluri *et al*. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/L. H./
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648